Marlboro
PM: MARL/02/03
MDSPS: AA05796

Informed Consent

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A 24-WEEK, RANDOMIZED, CONTROLLED STUDY TO EVALUATE EXPOSURE TO SMOKE CONSTITUENTS OF MARLBORO LIGHTS AND MARLBORO ULTRA LIGHTS COMPARED TO MARLBORO (FULL FLAVOR) CIGARETTES IN ADULT SMOKERS DURING UNRESTRICTED SMOKING

Principal Investigator: James C. Kisicki, M.D.
MDSPS Project No: AA05796

Giving false, incomplete, or misleading information about your medical history, including past and present usage of medications, could have very serious consequences for your well being. It is vitally important that you provide a true and complete medical history.

Please read this form carefully and do not hesitate to ask the study physician any questions about this form and/or the information provided in it.

A. INTRODUCTION/PURPOSE

You are being asked to participate in a research study evaluating long-term exposure to the compounds that make up the smoke of cigarettes in adult smokers during unrestricted smoking. This evaluation will be conducted by measuring identified biomarkers from cigarette smoke constituents in blood and urine. A biomarker is a biological substance or biological effect, which can be measured to evaluate a relationship between a foreign substance such as cigarette smoke and a body process.

This study is not intended to assess any medical treatment and, thus, alternative treatment is not appropriate. The only alternative to participating is not to participate. You will receive no medical benefit from your participation in this study. There are no costs to you for participating in the study. All study supplies and study procedures are provided to you at no cost.

B. STUDY DESCRIPTION

Selected biomarkers in the blood and urine will be analyzed throughout the study. Initially, up to 120 healthy male and female adult volunteers who participated in the prior study [MARL/01/03 (AA05624)] will be enrolled in the study.

SCREENING VISIT:
There will be no screening visit for this study. The screening information and information collected during the prior study (MARL/01/03) will be used to determine if you are eligible for this study. By signing this document, you are granting permission to MDS Pharma Services and

the study sponsor to review your confidential information collected during the prior study (MARL/01/03) in order to make an eligibility determination.

CLINIC CONFINEMENT/GROUP RANDOMIZATION:

You will receive a detailed time-and-events schedule. The study covers a study period of approximately 24 weeks. You will be required to visit the clinic on 12 occasions during the study period.

If you are enrolled in this long-term continuation study, you will finish all events of the prior short-term study (MARL/01/03) and have some additional blood samples taken and tests of your final urine collection done. You will then be required to report to the clinic in a fasted state (no food or beverages, except water, for 8 hours) for scheduled events at Weeks 4, 8, 12, 16, 20, and 24. In addition, you will visit the clinic at Weeks 2, 6, 10, 14, 18, and 22 to replenish your supply of cigarettes and return empty cigarette packages. Prior to the Week 4, 8, 12, 16, 20, and 24 visits, you will be required to collect your urine over a 24-hour interval in your usual community setting and bring the collected urine to the clinic with you at each scheduled visit.

During this study, you will remain in the same group you were randomized to for the prior study (MARL/01/03).

Group A	**Marlboro**
Group B	**Marlboro LIGHTS**
Group C	**Marlboro ULTRA LIGHTS**

Following conclusion of the prior short-term study (MARL/01/03), you will be given a 2-week supply of study cigarettes. You will be permitted to smoke the assigned study cigarette as you desire and will be required to smoke it as your exclusive brand throughout this long-term continuation study. You will be required to save all empty study cigarette packages and return them to the clinic staff at 2-week intervals. Your supply of cigarettes will be replenished at each of these visits and study compliance will be monitored.

You will be required to maintain a diary, provided by the staff, while participating in the study. You will document the number of study cigarettes smoked each day, time smoked, and any non-study cigarettes (number, time, and brand name) you may have smoked.

During the study, you will never be required to smoke ~~by the study staff.~~ In addition, you may choose to quit smoking at any time. **Subjects who elect to quit smoking may do so and will continue in their assigned group and will finish the study according to that group's schedule.** If you are randomized to Group A, you will be permitted to smoke only Marlboro cigarettes King Size, Filter Hard Pack (hereinafter referred to as Marlboro) cigarettes for the duration of the study. If you are randomized to Group B, you will be permitted to smoke only Marlboro LIGHTS cigarettes for the duration of the study. If you are randomized to Group C, you will be permitted to smoke only Marlboro ULTRA LIGHTS cigarettes for the duration of the study.

Smoking Topography

Your puffing profile (topography) will be measured by a device designed to collect this information (CReSSmicro™ portable measurement device). During your 24-hour urine collection prior to the Week 4, 8, 12, 16, 20, and 24 visits, your first cigarette of the day and one cigarette between dinnertime and bedtime (preferably the first cigarette after dinner) will be smoked using the CReSSmicro™ portable measurement device. You will bring the measurement

device with you to the clinic at the Week 4, 8, 12, 16, 20, and 24 visits for downloading of your smoking topography information.

Urine Collection

During the study, you will collect your urine for biomarker analysis during a 24-hour interval just prior to the Week 4, 8, 12, 16, 20, and 24 clinic visits. Containers, coolers, and refrigerant gel packs for these collections will be provided to you. You will bring your 24-hour urine collections with you to the clinic the next day, at each of these visits.

Questionnaires

You will complete a Diet, Consumption, and Physical Activity Questionnaire, a Product Assessment Questionnaire, a Smoking Behavior Questionnaire at the Week 4, 8, 12, 16, 20, and 24 visits.

Clinical Examinations

You will be evaluated with clinical laboratory tests, physical examinations, weight, ECGs (a recording of the electrical activity of the heart), and vital sign measurements (blood pressure, pulse rate, respiratory rate, and oral temperature) at selected visits throughout the study. Smoking will be prohibited for at least 15 minutes prior to each vital signs measurement. For the Weeks 4, 8, 12, 16, 20, and 24 visits, you will report to the clinic after an overnight fast (no food or beverages, except water, for 8 hours) for the required blood and urine collections.

C. BLOOD COLLECTION

In this study, blood samples will be collected for clinical laboratory tests and biomarker analysis at Weeks 0, 4, 8, 12, 16, 20 and 24 for a total of approximately 155 mL (6 ounces) requiring approximately 6 venipunctures (insertion of needle into vein). Some of the blood samples taken on Day –1 and Day 8 for the prior study (MARL/01/03) will be used for analysis in this study. If necessary for safety evaluations, additional samples may be collected.

D. POTENTIAL RISKS/ADVERSE EFFECTS OF STUDY PROCEDURES:

Potential adverse effects of pulmonary function tests include shortness of breath and dizziness.

The risks involved in drawing blood (venipuncture) include pain, discomfort, infection, bleeding and/or bruising at the puncture site, and fainting.

There is always the possibility that some unexpected adverse effect may develop in some persons participating in the procedures in this study. Trained medical personnel are available at MDS Pharma Services to provide immediate medical attention if required.

Cigarette smoking during pregnancy is associated with increased risk of spontaneous abortion, low birth weight infants, and prenatal mortality. Therefore, pregnant women cannot participate in this study, and women of childbearing potential must avoid becoming pregnant during the study. Nicotine passes freely into breast milk, and a nursing child may receive nicotine from a smoking mother's milk with the possibility of causing harmful side effects to the child. Therefore, women who are nursing cannot participate in this study.

Any significant or new findings that develop during the course of this study that may relate to your willingness to continue participation will be provided to you in writing in a timely manner.

E. REQUIREMENTS AND INSTRUCTIONS

Participation in this study requires that:

- You participated and completed the prior study (MARL/01/03).
- You are generally healthy as determined by medical history, physical examination, ECG, pulmonary function testing, and clinical laboratory tests from the prior study (MARL/01/03) unless deemed not clinically significant by the study physician and/or study Sponsor.
- You are an adult between 21 and 65 years of age (inclusive) and have a smoking history of manufactured non-menthol cigarettes of between 10 and 30 cigarettes per day for 12 months prior to enrollment in the prior study (MARL/01/03).
- You have smoked Marlboro cigarettes (Kings, hard pack or soft pack) as your exclusive brand for a minimum of 4 weeks prior to enrollment in the prior study (MARL/01/03).
- You have not used any other nicotine or tobacco-containing product other than manufactured cigarettes (including roll-your-own cigarettes, bidis, snuff, nicotine inhaler, pipe, cigar, chewing tobacco, nicotine patch, nicotine spray, nicotine lozenge, or nicotine gum) within 4 weeks prior to enrollment in the prior study (MARL/01/03).
- You are capable of understanding and willing to sign this Informed Consent Form.

The study physician will review the findings from medical/medication history, physical examinations, clinical laboratory tests, pulmonary function tests, ECG, and vital signs from screening and during your participation in the prior study (MARL/01/03) to determine your eligibility for this study. Following the review by the study physician and/or study Sponsor, you will be declined entry into the study for any of the following reasons (the list is not all-inclusive):

- You have a clinically significant history or evidence (*i.e.*, findings from physical examination, vital signs, clinical laboratory tests, pulmonary function tests, ECG) of disease or abnormalities of any of the following body systems/body organs that, in the opinion of the study physician, would jeopardize your safety or impact the validity of the study results:
  - **Gastrointestinal** – related to the stomach/intestines, including conditions such as bleeding ulcers, inflammatory bowel disease, etc.
  - **Renal** – related to the kidneys, including conditions such as kidney stones, etc.
  - **Hepatic** – related to the liver, including conditions such as cirrhosis, hepatitis, jaundice, etc.
  - **Endocrine** – related to gland function, including conditions such as diabetes, thyroid disorders, etc.
  - **Oncologic** – related to cancers.
  - **Pulmonary** – related to the lungs/breathing, including conditions such as chronic obstructive pulmonary disease and tuberculosis, etc.
  - **Cardiovascular** – related to the heart and blood circulation system, including conditions such as heart attack, abnormal ECG, chest pain, congestive heart failure, etc.
  - **Neurological** – related to the brain and spinal cord, including conditions such as epilepsy, stroke, multiple sclerosis, seizures, etc.
  - **Psychiatric** – related to the brain in terms of behavior/emotions, including conditions such as depression, and addictions such as eating disorders, drug abuse, alcohol abuse, etc.
  - **Hematological** – related to the blood, including conditions such as anemia, clotting disorders, etc.
  - **Immunological** – related to the immune system, including conditions such as autoimmune diseases, AIDS, etc.
- You have any history (current or past) of congestive heart failure.
- You had an active fever of greater than 100.2°F at screening or at check-in for the prior study (MARL/01/03).

- You had an acute (sudden onset) illness (*e.g.*, upper respiratory infection, viral infection) requiring treatment within 2 weeks prior to initiation of the prior study (MARL/01/03).
- You had donated blood of 1 pint or more or received a whole blood or blood product transfusion within 56 days prior to initiation of the prior study (MARL/01/03).
- You had donated plasma within 7 days prior to initiation of the prior study (MARL/01/03).
- You have diabetes mellitus that cannot be controlled by diet and exercise alone (*i.e.*, requires treatment with prescription anti-diabetic medication or insulin therapy).
- You require treatment with prescription or over-the-counter bronchodilator medications (*e.g.*, inhaled or oral β-agonists).
- You have a history of alcohol and/or drug abuse within the 12 months prior to initiation of the prior study (MARL/01/03).
- You have participated in a previous clinical study for an investigational drug, device, or biological product within 30 days prior to the study with the exception of participation in the prior study (MARL/01/03).
- You have a positive urine screen for drugs of abuse.
- You or a first-degree relative (parent, sibling, child) are a current or former employee of the tobacco industry or a named party or class representative in litigation with Philip Morris USA.
- You or a first-degree relative are a current employee of MDS Pharma Services.
- If female, you are pregnant or nursing, or intend to become pregnant from screening through completion of the study.
- Your carboxyhemoglobin level at screening or check-in for the prior study (MARL/01/03) indicates that you are not a smoker.
- You are considered a puffer (a smoker who draws smoke from the cigarette into the mouth and throat, but does not inhale).

Restrictions For the Study

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- Smoke only the cigarettes provided during the study.
- Do not engage in strenuous exercise for 48 hours prior to each scheduled clinic visit at Weeks 4, 8, 12, 16, 20 and 24.
- Do not donate blood or blood products (including plasma) while enrolled in the study.
- If you are a woman of childbearing potential (*i.e.*, not surgically sterile by hysterectomy or tubal ligation at least 6 months prior to study initiation or at least 2 years naturally postmenopausal) and sexually active, you must agree to use one of the following methods of birth control:
    - hormonal (*i.e.*, oral, transdermal patch, implant, or injection) consistently for at least 3 months prior to initiation of the previous study (MARL/01/03) and throughout this study,
    - double barrier (*i.e.*, condom with spermicide or diaphragm with spermicide) consistently for at least 2 weeks prior to initiation of the previous study (MARL/01/03) and throughout this study,
    - IUD for at least 2 weeks prior to screening of the previous study (MARL/01/03) and throughout this study, or
    - have a partner who has been vasectomized for at least 6 months prior to initiation of the previous study (MARL/01/03).

Females must also accept the risk that pregnancy might result even while using these methods of birth control.

F. CONFIDENTIALITY

Information collected during the study will be considered confidential and will be retained in a secure database by MDS Pharma Services and the study Sponsor. All of this confidential information is subject to review by the appropriate staff and representatives on behalf of the

Sponsor, the Institutional Review Board, and possibly regulatory authorities, for verification of clinical procedures and/or data. Your permission for such review of your confidential information is granted by signing this document. For purposes of study reporting, you will be identified by initials and numbers only. However, your name, address, telephone number, and an individual to contact in case of an emergency will be kept in the record of the study physician at MDS Pharma Services in case you need to be contacted in the future about this study. Where required by law or statute, some medical results will be reported to health authorities. The results of this study may be published but will not disclose your identity.

G. ACKNOWLEDGMENT

I understand that:

- At the conclusion of the study, regardless of whether I have chosen to smoke or quit smoking during the study, MDS Pharma Services will pay me up to $ 4,000 by check for my participation in this study. If for any reason I do not complete the study (*i.e.,* I am dropped by the study physician and/or Sponsor, I am dropped for not following the directions/instructions of the study staff, I choose to discontinue, or the study is discontinued by the study physician and/or Sponsor), I will be paid on a prorated basis. No deductions for any state or federal withholding or any other similar taxes will be made. I am solely responsible for reporting such payment on my state and federal tax returns and for the payment of any taxes due for the receipt of these payments from MDS Pharma Services.
- To reduce the health effects of smoking, the best thing to do is to quit smoking.
- Participating in this study does not make me an employee of the Sponsor or MDS Pharma Services.
- While involved in this study, I will have direct access to medical attention.
- If I become physically injured or ill as a direct result of participation in this research study, MDS Pharma Services will provide the medical treatment necessary to assist in my recovery from the injury or illness. There will be no charge to me for this care beyond what is covered by my health insurance. This agreement to provide free medical treatment does not include treatment for any illness or injury I might experience during the course of the study if the illness or injury is not the result of the research study. No compensation other than free medical treatment of the injury or illness will be provided.
- Provision of medical treatment shall not be an admission by MDS Pharma Services, or the Sponsor that my injury or illness is study related.
- If I experience an adverse reaction or injury while participating in this research study, I will contact MDS Pharma Services' 24-hour Nurse's Line by calling **(402) 790-4742**. If I wish to contact the physician in charge of this study, I will call **Dr. James C. Kisicki** at **(402) 476-2811** or, if after 4:30 p.m. or on weekends, at **(402) 610-0111**. Since the physician may not always be immediately available, the 24-hour Nurse's Line should be utilized.

H. CONSENT

I have read this written informed consent document and freely consent to participate in this study.

I understand:

- The nature of the study.
- I am a voluntary subject.
- The physician in charge can remove me from the study without my consent, either because of my failure to follow the study requirements or if the physician feels it is medically in my best interest.
- The study includes examinations, including blood examinations, to which I will be subjected.
- The Sponsor may stop the study, or discontinue my participation, at any time at its discretion.

- The study includes examinations, including blood examinations, to which I will be subjected.
- The Sponsor may stop the study, or discontinue my participation, at any time at its discretion.
- Procedures in this study may be associated with undesirable effects, some of which may not be known.
- I may choose to withdraw from the study at any time.
- I may refuse to participate or withdraw from participation at any time without penalty or loss of benefits to which I am otherwise entitled (I may be paid for my participation on a prorated basis.).
- Nothing contained in this informed consent waives any of my legal rights as a volunteer, nor does it release the study physician, the Sponsor, MDS Pharma Services or its agents from any liability for negligence.

I agree to adhere to the regulations and directions of the study as outlined. I have been told how long and by what methods the study will be carried out, and I have been reminded that I have the opportunity to ask further questions about the details and procedures of the study.

All my questions have been satisfactorily answered. I have received a signed and dated copy of this consent form.

If I have any further questions regarding my rights as a volunteer, I will contact Frank E. Landis Jr., J.D., of the MDS Pharma Services Institutional Review Board at 1-800-776-1716.

If I have any further questions about the study, I will contact MDS Pharma Services' 24-hour Nurse's Line by calling (402) 790-4742.

II. CERTIFICATION

I certify that I am between 21 and 65 years of age (inclusive) and have no known existing undisclosed medical problems.

I certify that I understand and meet the requirements for study participation as outlined in Section E (Requirements and Instructions), and will adhere to instructions of the study staff during the course of the study.

My signature below certifies that I understand the research investigation discussed above.

If female, I certify that I am not pregnant and not nursing.

Witness my signature this _____ day of _____ 20 __

Print Name: _____ Signature: _____

Person Administering Informed Consent: _____ (Print) _____ (Signature)

Date: _____ Time:_____ MDS Pharma Services ID No.: _____